产品名称：**CHIR-124**
产品别名：**CHIR-124**

生物活性：

Description	CHIR-124 is a potent and selective Chk1 inhibitor with IC_{50} of 0.3 nM, and also potently targets PDGFR and FLT3with IC_{50}s of 6.6 nM and 5.8 nM.

IC_{50} & Target

Chk1	PDGFR	Chk2	FLT3	Cdk4/cyclin D
0.3 nM (IC_{50})	6.6 nM (IC_{50})	697.4 nM (IC_{50})	5.8 nM (IC_{50})	2.05 μM (IC_{50})
CDC2/cyclin B	Cdk2/cyclin A	bFGFR	FGFR3	VEGFR2 FLK1
0.5057 μM (IC_{50})	0.1911 μM (IC_{50})	2.01 μM (IC_{50})	1.29 μM (IC_{50})	0.5779 μM (IC_{50})
VEGFR1 FLT1	PKCα	PKAβ I	PKCβ II	PKCγ
0.4636 μM (IC_{50})	0.58 μM (IC_{50})	2.25 μM (IC_{50})	0.58 μM (IC_{50})	0.11 μM (IC_{50})
ERK2	PKA	GSK3		
4.31 μM (IC_{50})	0.1031 μM (IC_{50})	0.0233 μM (IC_{50})		

In Vitro	CHIR-124 is 500- to 5,000-fold less active against other cell cycle kinases, such as cyclin-dependent kinase 2/cyclin A (0.19 μM), cdc2/cyclin B (0.51 μM), and cyclin-dependent kinase 4/cyclin D (2.1 μM). CHIR-124 (≥0.9 nM) in combination with SN-38 (≥0.42 nM) causes significant synergy or >10% deviation from additivity in human cancer cell lines expressing mutant p53, and these values overlap and fall below the IC_{50}s for SN-38 (1.2×10^{-7} M) and CHIR-124 (2.2×10^{-7} M), respectively. Moreover, CHIR-124 (100 nM) abrogates the SN-38-induced S and G2-M phase cell cycle checkpoints. CHIR-124 (200 nM) leads to a 2.5-fold elevated level of cdc25A above that of the untreated HCT116 $p53^{-/-}$ cells. The down-regulation of cdc25A induced by SN-38 is completely restored by concurrent or sequential treatment with CHIR-124, proving that CHIR-124 inhibits the Chk1-mediated destruction of cdc25A in whole cells[1]. CHIR-124 occupies the ATP-binding site, inhibits Chk1 (IC_{50}, 0.3 nM) 2,000-fold more potently than Chk2 (IC_{50}, 0.7 μM)[2].
In Vivo	CHIR-124 (10 or 20 mg/kg, p.o.) does not have a significant effect on tumor growth when compared with the vehicle-treated group, but it potentiates the growth inhibitory effect of CPT-11 in a human breast carcinoma xenograft model. The potentiation of the tumor growth inhibitory effect of CPT-11 by CHIR-124 is associated with an increase in apoptosis induction in the tumors. CHIR-124 reverses the suppression of phospho-H3 staining induced by CPT-11, indicating abrogation of the G2-M checkpoint by CHIR-124[1].

Solvent&Solubility

In Vitro:

DMSO : 14 mg/mL (33.34 mM; Need ultrasonic and warming)

Preparing Stock Solutions	Solvent / Mass / Concentration	1 mg	5 mg	10 mg
	1 mM	2.3815 mL	11.9073 mL	23.8146 mL
	5 mM	0.4763 mL	2.3815 mL	4.7629 mL
	10 mM	0.2381 mL	1.1907 mL	2.3815 mL

*请根据产品在不同溶剂中的溶解度选择合适的溶剂配制储备液；一旦配成溶液，请分装保存，避免反复冻融造成的产品失效。

储备液的保存方式和期限：-80°C, 6 months; -20°C, 1 month。-80°C 储存时，请在 6 个月内使用，-20°C 储存时，请在 1 个月内使用。

[1]. Tse AN, et al. CHIR-124, a novel potent inhibitor of Chk1, potentiates the cytotoxicity of topoisomerase

References	I poisons in vitro and in vivo. Clin Cancer Res, 2007, 13(2 Pt 1), 591-602. [2]. Dai Y, et al. New insights into checkpoint kinase 1 in the DNA damage response signaling network. Clin Cancer Res, 2010, 16(2), 376-383.

实验参考：

Animal Administration	Severe combined immunodeficient mice harboring MDA-MD-435 tumor xenografts are randomized into the following treatment groups of 10: vehicle (captisol) alone, 5 mg/kg CPT-11, 10 mg/kg CHIR-124, 20 mg/kg CHIR-124, 5 mg/kg CPT-11 plus 10 mg/kg CHIR-124, or 5 mg/kg CPT-11 plus 20 mg/kg CHIR-124. Treatment is initiated on the day after randomization (day 1). CPT-11 is given i.p. daily (four times daily) ×5 on days 1 to 5, whereas CHIR-124 is given orally four times daily ×6 on days 2 to 7 in captisol. Percent tumor growth inhibition is defined as % T/C, where T = the treatment group mean, and C = the control group mean. In a similar study, tumors harvested from mice sacrificed on day 4 of treatment are examined for apoptosis by terminal deoxynucleotidyl transferase-mediated nick-end labeling staining and for mitotic index by immunofluorescence labeling with phospho-histone H3 antibody. [1]
Kinase Assay	For the CHK1 assay, the kinase domain is expressed in Sf9 insect cells, and a biotinylated cdc25c peptide containing the consensus Chk1/Chk2 phosphorylation site (*)(biotin-[AHX]SGSGS*GLYRSPSMP-ENLNRPR[$CONH_2$]) is used as the substrate. A dilution series of CHIR-124 is mixed with a kinase reaction buffer containing a final concentration of 30 mM Tris-HCl (pH 7.5), 10 mM $MgCl_2$, 2 mM DTT, 4 mM EDTA, 25 mM β-glycerophosphate, 5 mM $MnCl_2$, 0.01% bovine serum albumin, 1.35 nM CHK1 kinase domain, 0.5 μM peptide substrate, and 1 μM unlabeled ATP, plus 5 nM ^{33}P γ-labeled ATP (specific activity =2,000 Ci/mmol). Reactions and detection of the phosphate transfer are carried out by a radioactive method. [1]
References	[1]. Tse AN, et al. CHIR-124, a novel potent inhibitor of Chk1, potentiates the cytotoxicity of topoisomerase I poisons in vitro and in vivo. Clin Cancer Res, 2007, 13(2 Pt 1), 591-602. [2]. Dai Y, et al. New insights into checkpoint kinase 1 in the DNA damage response signaling network. Clin Cancer Res, 2010, 16(2), 376-383.